AMENDMENTS TO THE FIGURES:

Please replace Figure 9 in the above-captioned application with the attached replacement Figure 9, labeled "Replacement Sheet," in compliance with 37 C.F.R. §1.84. Applicants submit that no new matter has been added to the drawing.

AMENDMENTS TO THE SEQUENCE LISTING:

Please replace the Sequence Listing in the above-captioned application with the attached substitute Sequence Listing. Annotated substitute sheets of SEQ ID NOS: 200, 203, 206, 290-311, 312-361, 401-428, 499-542, 1043, and 1306 are included herein to point out the amendments made herein to the sequence listing. Applicants assert that the application is in compliance with 37 C.F.R. §§ 1.821-1.825 and that no new matter has been added.

REMARKS

Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 06-1050.

IN THE SPECIFICATION:

Amendments to the specification include amendments to the Description of the Figures to bring the specification into compliance with the Sequence Rules set forth in 37 C.F.R. §§ 1.821-1.825. Additional amendments seek to correct inadvertent errors in references to SEQ ID NO identifiers used in the specification. Further amendments correct minor errors to produce grammatical clarity.

Amendments to pages 11-14 incorporate SEQ ID NO identifiers to the Description of the Figures to correctly reference the Sequence Listing in compliance with the Sequence Rules set forth in 37 C.F.R. §§ 1.821-1.825. In addition, the Description of the Figures also have been amended to specify the particular residues of the respective protein sequence referenced within the Figures as compared to the sequences provided in the Sequence Listing. These amendments find basis in the Figures as originally filed (and in the case of Figure 9, *as amended herein*) and in the Sequence Listing as originally filed (and in the case of IL-10 (SEQ ID NO: 200), SCF (SEQ ID NO: 206), and Flt3 ligand (SEQ ID NO: 203), *as amended herein*). For example, the amendment to the paragraph beginning on page 11, line 11 incorporates the SEQ ID NO identifiers for the sequences for IFN-α2b, IFNβ, EPO, and G-CSF described in FIG. 9 of the drawings.

Amendments to the paragraph beginning on page 11, line 29 incorporates the SEQ ID NO identifiers 989-1015 and 1016-1302 of the Sequence Listing which, in addition to the SEQ ID NO identifiers 233-289 already listed, provide a complete listing of all of the modified protein sequences of interferon β represented in the Sequence Listing. In addition, the paragraph on page 11, line 29 also is amended to recite "a representative number of" in order to correctly reflect that the listed substitutions 1-57 in FIG. 12A are not the only modified interferon β is-HITs, but rather are representative of modified interferon β sequences as specified by SEQ ID NOS: 233-289, 989-1015, and 1016-1302. Basis for this amendment can be found in the specification at page 99, line 1 through page 112, line 31 which lists the is-HIT target positions on IFNβ, based on the mature protein sequence of

IFNB depicted by SEQ ID NO: 196. Amendments to the paragraph beginning on page 11, line 29 also incorporates the SEQ ID NO identifier for the wild-type sequence of Interferon β depicted in Fig. 12A and specified by SEQ ID NO:196.

Amendments to the paragraph beginning on page 12, line 3 incorporates the SEQ ID NO identifier for the wild-type sequence of interferon gamma and specifies the residues of the interferon gamma sequence depicted in Fig. 12B as specified by SEQ ID NO: 199. Amendments to the paragraph beginning on page 12, line 7 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-10 and specifies the residues of the interleukin-10 sequence depicted in Fig. 12C as specified by SEQ ID NO: 200 *as amended herein*. Amendments to the paragraph beginning on page 12, line 11 incorporates the SEQ ID NO identifier for the wild-type sequence of ciliary neurotrophic factor and specifies the residues of the ciliary neurotrophic factor sequence depicted in Fig. 12D as specified by SEQ ID NO:212. Amendments to the paragraph beginning on page 12, line 15 incorporates the SEQ ID NO identifier for the wild-type sequence of granulocyte-colony stimulating factor and specifies the residues of the granulocyte-colony stimulating factor sequence depicted in Fig. 12E as specified by SEQ ID NO:210. Amendments to the paragraph beginning on page 12, line 19 incorporates the SEQ ID NO identifier for the wild-type sequence of human growth hormone and specifies the residues of the human growth hormone sequence depicted in Fig. 12F as specified by SEQ ID NO:216. Amendments to the paragraph beginning on page 12, line 23 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-12 and specifies the residues of the interleukin-12 sequence depicted in Fig. 12G as specified by SEQ ID NO:215. Amendments to the paragraph beginning on page 12, line 27 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-6 and specifies the residues of the interleukin-6 sequence depicted in Fig. 12H as specified by SEQ ID NO:217. Amendments to the paragraph beginning on page 13, line 1 incorporates the SEQ ID NO identifier for the wild-type sequence of leptin as depicted in Fig. 12I and specified by SEQ ID NO:211. Amendments to the paragraph beginning on page 13, line 5 incorporates the SEQ ID NO identifier for the wild-type sequence of leukemia inhibitory factor and specifies the residues of the leukemia inhibitory factor sequence depicted in Fig. 12J as specified by SEQ ID NO:213. Amendments to the paragraph beginning on page 13, line 9 incorporates the SEQ ID NO identifier for the wild-type sequence of oncostatin M and

specifies the residues of the oncostatin M sequence depicted in Fig. 12K and specified by SEQ ID NO:214. Amendments to the paragraph beginning on page 13, line 13 incorporates the SEQ ID NO identifier for the wild-type sequence of erythropoietin as depicted in Fig. 12L and specified by SEQ ID NO:201. Amendments to the paragraph beginning on page 13, line 17 incorporates the SEQ ID NO identifier for the wild-type sequence of Flt3 ligand and specifies the residues of the Flt3 ligand sequence depicted in Fig. 12M as specified by SEQ ID NO:203 *as amended herein*. Amendments to the paragraph beginning on page 13, line 21 incorporates the SEQ ID NO identifier for the wild-type sequence of granulocyte-macrophage colony-stimulating factor as depicted in Fig. 12N and specified by SEQ ID NO:202. Amendments to the paragraph beginning on page 13, line 25 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-13 as depicted in Fig. 12O and specified by SEQ ID NO:209. Amendments to the paragraph beginning on page 13, line 29 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-2 as depicted in Fig. 12P and specified by SEQ ID NO:204. Amendments to the paragraph beginning on page 14, line 3 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-3 as depicted in Fig. 12Q and specified by SEQ ID NO:205. Amendments to the paragraph beginning on page 14, line 7 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-4 as depicted in Fig. 12R and specified by SEQ ID NO:207. Amendments to the paragraph beginning on page 14, line 11 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-5 as depicted in Fig. 12S and specified by SEQ ID NO: 208. Amendments to the paragraph beginning on page 14, line 15 incorporates the SEQ ID NO identifier for the wild-type sequence of stem cell factor and specifies the residues of the stem cell factor sequence depicted in Fig. 12T as specified by SEQ ID NO:206 *as amended herein*.

Amendment to the paragraph on page 61, line 8-9 moves the position of the SEQ ID NO identifier (SEQ ID NO:1) in the sentence to improve clarity. SEQ ID NO:1 is the sequence identifier for the amino acid sequence of IFNα-2b which finds basis at page 1 of the Sequence Listing and throughout the specification, such as at page 69, lines 9-10. Since the amended sentence at page 61, lines 8-9 refers to both the mature peptide IFNα-2b and the nucleotides which encode that peptide, the SEQ ID NO:1 has been moved so that it is clear that the identifier refers to the protein sequence and not the nucleotide sequence of IFNα-2b.

No new matter has been added to the specification.

IN THE CLAIMS:

Claims 1-77 and 82-331 are pending in this application. Claims 78-81 are canceled herein without prejudice or disclaimer. Applicants reserve the right to prosecute any canceled subject matter in a continuing application. Claims 2, 3, 6-9, 12, 14, 15, 18-20, 24, 33, 41-43, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 77, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120, 122, 123, 125, 126, 128, 129, 131, 132, 134, 135, 137, 138, 254, 280, 286-288, 306-308, 310, 315-317, 321, 328-331 are amended herein. Support for the amendments to claims 76, 83, 86, 89, 92, 95, 98, 101, 104, 107, 113, 116, 119, 122, 125, 128, 131, 134 and 137 can be found throughout the specification as filed. See, for example, lines 20-24 of page 35, lines 10-15 of page 74 and lines 1-5 of page 75 of the specification. All other claims are amended to correct grammatical errors and do not alter the substance of the claims.

No new matter has been added to the claims.

IN THE FIGURES:

Attached herewith is a replacement drawing of Fig. 9, labeled "Replacement Sheet," in compliance with 37 C.F.R. §1.84. Amendments to the Figures include amendments to Fig. 9 to correct the sequence of G-CSF depicted within Fig. 9. The sequence of G-CSF depicted in Fig. 9 inadvertently is missing several amino acid residues. Fig. 9 is amended herein to correct these inadvertent errors by amending the sequence to add in the first three amino acids, Thr Pro Leu (TPL), of the mature protein sequence and also to add three amino acids, Val Ser Glu (VSE), corresponding to position 36-38 of the wild-type sequence of G-CSF as depicted in SEQ ID NO: 210 of the Sequence Listing. Basis for this amendment can be found within SEQ ID NO: 210 of the Sequence Listing as originally filed. SEQ ID NO: 210 is described in the specification at page 6, line 2 as granulocyte colony stimulating factor (G-CSF). As further support for the amendment, the sequences of the other cytokines depicted within Fig. 9, (e.g., IFN-α2b, IFN-β, and EPO) are the exact wild-type sequences of the respective cytokines as specified in the Sequence Listing and pertain to SEQ ID NOS: 1, 196, and 201, respectively.

No new matter has been added to the Figures.

IN THE SEQUENCE LISTING:

Attached herewith are a substitute Sequence Listing, marked-up paper copies of SEQ ID NOS: 200, 203, 206, 290-311, 312-361, 401-428, 499-542, and 1043 indicating the changes made, and a verified statement that the content of the computer-readable copy and the substitute Sequence Listing are the same in accordance with 37 C.F.R. §§1.821-1.825.

Amendments to the Sequence Listing include amendments at page 99 of the Sequence Listing to correct a typographical error in the Numeric identifier (<308>) of SEQ ID NO: 200. The database accession number was inadvertently listed as "Genbank NP_00063" and is amended herein to be "Genbank NP_000563." Basis for this amendment can be found within the specification at page 5, line 29 where SEQ ID NO: 200 is described as interleukin-10. One of ordinary skill in the art would recognize that Genbank NP_00063 is obviously incorrect as it is not a complete accession number, whereas Genbank NP_000563 is a complete accession number that correctly identifies the sequence of the interleukin 10 (IL-10) precursor sequence including the mature protein sequence representing amino acids 19-178 of the precursor IL-10. Further, although the database entry date (<309>) of 2000-10-31 in the sequence listing for Genbank NP_000563 has changed to 2005-06-21, a person of ordinary skill in the art would recognize that the sequence for IL-10 listed in Genbank NP_000563 is not different from earlier known sequences for IL-10. For instance, in the "Comment" section of the entry data for Genbank NP_000563 it states that "the reference sequence was derived from M57627.1 and BC022315.1". Genbank M57627.1 is the nucleotide sequence for IL-10 with a database entry date of 1995-03-07 and links to Genbank AAA63207 which is the protein sequence of IL-10 also with an entry date also of 1995-03-07. The database accession numbers NP_000563 and AAA63207 depict the exact same sequence for a precursor IL-10 protein of 178 amino acids and a mature protein sequence representing amino acids 19-178 of the precursor IL-10. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at line 29 of page 5 and the Sequence Listing at page 99 with respect to IL-10, Applicant intent at the time of filing was to reference the Genbank NP_000563 sequence. Therefore, the correction of the typographical error in the Genbank identifier does not introduce new matter.

The Numeric identifier (<308>) of SEQ ID NO: 206 on page 101 of the Sequence Listing also is amended herein to correct a typographical error. The database accession number was inadvertently listed as "Genbank AAA85480" and is amended herein to be "Genbank AAA85450." Basis for this amendment can be found within the specification at page 6, line 12 where SEQ ID NO: 206 is described as stem cell factor (SCF). One of ordinary skill in the art would recognize that Genbank AAA85480 is obviously incorrect as this references a bacterial gene product of 17 amino acids, whereas Genbank AAA85450 correctly identifies the sequence of the SCF precursor sequence including the mature protein sequence representing amino acids 26-273 of the precursor SCF. Further, the database entry date (<309>) of 1996-01-19 listed in the sequence listing for Genbank AAA85450 has not changed. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at line 12 of page 6 and the Sequence Listing at page 101 with respect to stem cell factor, Applicant intent at the time of filing was to reference the Genbank AAA85450 sequence. Therefore, the correction of the typographical error in the Genbank identifier does not introduce new matter.

SEQ ID NO. 200 at page 99 of the Sequence Listing and SEQ ID NOS: 312-361 on pages 143-159 of the Sequence Listing are amended to provide the full-length sequence corresponding to the mature IL-10 protein having 160 amino acids by adding the final 60 amino acids to the sequences. For reference, these changes are underlined on the paper copies of SEQ ID NOS: 200 and 312-361 provided herewith. Basis for this amendment can be found in the specification, at lines 14-20 of page 90,where SEQ ID NO: 200 is described in the specification as IL-10 and SEQ ID NOS: 312-361 are described as IL-10 sequences containing substitutions of the native amino acid sequence. Further support for this amendment can be found in the Sequence Listing on page 99, *as amended herein*, where the numeric identifier "<308>" specifies the Database Accession number as being "Genbank NP_000563." Genbank number NP_000563 sets forth an Interleukin 10 precursor protein wherein the mature protein is represented by amino acids 19-178 of the sequence, thereby designating a mature protein of 160 amino acids in length. Further, as discussed above, although the database entry date (<309>) of 2000-10-31 listed in the sequence listing for Genbank NP_000563 has changed, one of ordinary skill in the art would recognize that the sequence for IL-10 listed in Genbank NP_000563 is not different from earlier known

sequences for IL-10. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at lines 14-20 of page 90 and of the Sequence Listing at page 99, that the mature (native) amino acid sequence of the IL-10 amino acid sequence provided in Genbank NP_000563 was the intended sequence. Therefore, the addition of the last 60 amino acids to the sequences of SEQ ID NOS: 200 and 312-361 does not introduce new matter, but rather corrects the sequences to correspond to the complete mature protein sequence of 160 amino acids.

SEQ ID NO. 203 at page 100 of the Sequence Listing and SEQ ID NOS: 401-428 at pages 173-182 of the Sequence Listing are amended to provide the full-length sequence corresponding to the mature Flt3 ligand protein having 209 amino acids by adding the final 109 amino acids to the sequences. For reference, these changes are underlined on the paper copies of SEQ ID NOS: 203 and 401-428 provided herewith. Basis for this amendment can be found in the specification, at lines 5-11 of page 91, where SEQ ID NO: 203 is described in the specification as Flt3 ligand and SEQ ID NOS: 401-428 are described as Flt3 ligand sequences containing substitutions of the native amino acid sequence. Further support for this amendment can be found in the Sequence Listing on page 100 where the numeric identifier "<308>" specifies the Database Accession number as being "Genbank AAA19825." Genbank number AAA19825 sets forth a Flt3 ligand precursor protein wherein the mature protein is represented by amino acids 27-235 of the sequence, thereby designating a mature protein of 209 amino acids in length. Further, the database entry date (<309>) of 1994-07-19 listed in the sequence listing for Genbank AAA19825 has not changed. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at lines 5-11 of page 91 and of the Sequence Listing at page 100, that the mature (native) amino acid sequence of the Flt3 ligand amino acid sequence provided in Genbank AAA19825 was the intended sequence. Therefore, the addition of the last 109 amino acids to the sequences of SEQ ID NOS: 203 and 401-428 does not introduce new matter, but rather corrects the sequences to correspond to the complete mature protein sequence of 209 amino acids.

SEQ ID NO. 206 at page 101-102 of the Sequence Listing and SEQ ID NOS: 499-542 on pages 209-226 of the Sequence Listing are amended to provide the full-length sequence corresponding to the mature stem cell factor (SCF) protein having 248 amino acids by adding

the final 107 amino acids to the sequences. For reference, these changes are underlined on the paper copies of SEQ ID NOS: 206 and 499-542 provided herewith. Basis for this amendment can be found in the specification, at line 27 of page 91 through line 3 of page 92, where SEQ ID NO: 206 is described in the specification as SCF and SEQ ID NOS: 499-542 are described as SCF sequences containing substitutions of the native amino acid sequence. Further support for this amendment can be found in the Sequence Listing on page 101, *as amended herein*, where the numeric identifier "<308>" specifies the Database Accession number as being "Genbank AAA85450." Genbank number AAA85450 sets forth a SCF precursor protein wherein the mature protein is represented by amino acids 26-273 of the sequence, thereby designating a mature protein of 248 amino acids in length. Further, the database entry date (<309>) of 1996-01-19 listed in the sequence listing for Genbank AAA85450 has not changed. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at line 27 of page 91, through line 3 of page 92 and of the Sequence Listing at page 101, that the mature (native) amino acid sequence of the SCF sequence provided in Genbank AAA85450 was the intended sequence. Therefore, the addition of the last 107 amino acids to the sequences of SEQ ID NOS: 206 and 499-542 does not introduce new matter, but rather corrects the sequences to correspond to the complete mature protein sequence of 248 amino acids.

As further support for these amendments, other cytokines included in the Sequence Listing contain the same number of amino acids as represented by the mature protein as specified by the respective Genbank numeric identifier. For example, SEQ ID NO: 210, which sets forth the sequence of the mature G-CSF protein, specifies the numeric identifier (<308>) "Genbank CAA27168" at page 103 of the Sequence Listing and specifies the database entry date (<309>) of 1995-03-21. One of ordinary skill in the art would recognize that Genbank CAA27168, with an entry date of 1995-03-21, designates a G-CSF protein of 207 amino acids, whereby amino acids 1-30 represent the signal sequence and amino acids 31-207 represent the mature protein of 177 amino acids as set forth exactly in SEQ ID NO:210. The modified sequences of G-CSF corresponding to SEQ ID NOS: 631-662 also set forth a sequence of 177 amino acids which are described in the specification at page 92, lines 25-31 as being sequences comprising mutations of one or more amino acid residues of G-CSF set forth in SEQ ID NO:210.

SEQ ID NOS: 290-311 on pages 136-143 of the Sequence Listing are amended herein to add the final 46 amino acids of the mature protein of Interferon gamma as set forth in SEQ ID NO: 199 at pages 98-99 of the Sequence Listing. These amino acids were inadvertently omitted from SEQ ID NOS: 290-311, but are contained in the reference wild-type sequence of Interferon gamma depicted in SEQ ID NO: 199. For reference, these changes are underlined on the paper copies of SEQ ID NOS: 290-311 provided herewith. Basis for these amendments can be found in the specification, at lines 7-13 of page 90, where SEQ ID NO: 199 is described in the specification as Interferon gamma and SEQ ID NOS: 290-311 are described as modified Interferon gamma cytokines comprising mutations of one or more amino acid residues of Interferon gamma corresponding to amino acid substitutions in SEQ ID NO: 199. Thus, the sequences of SEQ ID NOS: 290-311 should be identical to the sequence of SEQ ID NO: 199 *except* for the point mutations at the positions listed on page 90 of the specification (*e.g.* 33, 37, 40, 41, 42, 58, 61, 64, 65, and 66). These substitutions are described in Fig. 12B as substitutions 1 through 21. Therefore, the addition of the last 46 amino acids to the sequences of SEQ ID NOS; 290-311 does not introduce new matter, but rather corrects the modified sequences of SEQ ID NOS: 290-311 to correspond to the reference wild-type sequence of Interferon gamma (SEQ ID NO: 199).

As further support for this amendment, other modified sequences in the Sequence Listing correspond exactly to their reference wild-type sequence *except* for point mutations introduced into the sequence at one or more amino acid position. For example, as described in the specification at lines 25-31 of page 92, and in the Sequence Listing at pages 103 and 257-272, SEQ ID NO: 210, which sets forth the 177 amino acid sequence for the mature protein G-CSF, is identical to the modified sequences of G-CSF corresponding to SEQ ID NOS: 631-662 *except* for the amino acid positions containing mutations.

SEQ ID NO: 1043 on page 454 of the Sequence Listing is amended to correct a typographical error whereby the sequence only listed 165 amino acids because the amino acid at position 166 was inadvertently omitted. Amino acid 166 has been added herein by amendment to be Asparagine (Asn). For reference, this change is underlined on the paper copy of SEQ ID NO: 1043 provided herewith. Basis for this amendment can be found in the specification at line 1 of page 99 through line 31 of page 112, where SEQ ID NO: 1043 is described as one of the modified Interferon beta cytokines comprising mutations of one or

more amino acid residues of Interferon beta corresponding to amino acid substitutions in SEQ ID NO: 196. Thus, the sequence of SEQ ID NO:1043 should be identical to the sequence of SEQ ID NO: 196 *except* for a point mutation at one of the positions listed on pages 99-112 of the specification. In the case of SEQ ID NO:1043, the point mutation is at amino acid position 22 where, compared to the reference SEQ ID NO:196 (*i.e.*, the mature wild-type sequence), the amino acid at position 22 has been changed from Tryptophan (W) to Histidine (H). Therefore, the addition of the last amino acid at position 166 to the sequence of SEQ ID NO: 1043 does not introduce new matter, but rather corrects the modified sequences of SEQ ID NO: 1043 to correspond to the reference wild-type sequence of Interferon beta (SEQ ID NO: 196).

In the preliminary amendment filed April 29, 2004, it was stated at page 4, lines 1-4 that "SEQ ID NO: 978 on page 523 and SEQ ID NO: 986 on page 528 of the Sequence Listing are amended to correct inadvertent typographical errors introduced in the sequence at amino acid position 158. Amino acid 158 is amended to Glycine (Gln) to replace Proline (Pro) in each of these sequences."

Amino acid 158 was amended to Gln to replace Pro as evidenced by the Sequence Listing. Applicant notes that it is well-known in the art that "Gln" is the three-letter abbreviation for Glutamine, not Glycine (Gly) such as disclosed in Table 1 of the specification. No changes have been made to SEQ ID NOS: 978 and 986.

In addition, the Title of Invention as specified by the <120> numeric identifier has been changed to reflect the correct title of the invention. This correction finds basis on the first page of the specification where the correct title of the invention is shown to be "Rational Evolution of Cytokines for Higher Stability, the Cytokines and Encoding Nucleic Acid Molecules."

No new matter has been added to the Sequence Listing.

The computer-readable copy of the Sequence Listing is entitled 922SEQ.004 and is identical to the substitute Sequence Listing. The replacement Sequence Listing does not contain new matter.

No new matter is made to any of the amendments to the specification, Claims, Figures, or Sequence Listing. Entry of this amendment and examination of the application are respectfully requested.

Respectfully submitted,

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APPENDIX

Attached herewith are:

1. Annotated paper copies of SEQ ID NOS: 200, 203, 206, 290-311, 312-361, 401-428, 499-542, 1043;
2. Substitute Sequence Listing;
3. Computer-readable copy of substitute Sequence Listing;
3. Verified Statement Pursuant to §1.821(f); and
4. Replacement Sheet of Fig. 9 Pursuant to §1.84.